Chapter 7

Effects of 5-fluorouracil adjuvant treatment of colon cancer

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Abstract

Since the late eighties and early nineties, 5-fluorouracil (5-FU) based chemotherapy is the standard adjuvant treatment for stage III colon cancer. After the initial introduction of 5-FU in standard treatment protocols, several changes have been made based on results of randomized studies on various treatment regimens, including new cytotoxic agents. In stage II patients, the role of adjuvant chemotherapy is debatable. However, there might be a role for adjuvant treatment in certain high-risk patients. Following a search of the Medline database, the authors review the results of randomized studies on 5-FU-based adjuvant therapy and discuss future therapeutic options.

Introduction

Overview of the disease

Colorectal carcinoma (CRC) is the most common gastro-intestinal malignancy and the second leading cause of cancer related deaths in the world. Each year, worldwide, 500 000 people die of the disease and nearly one million cases are newly diagnosed. The disease is relatively more common in the Western World. Both genetic factors and non-genetic factors, mostly related to the Western lifestyle, contribute to the pathogenesis of colon carcinoma. Genetic predisposition may have a very strong effect in the dominantly inherited cancer syndromes, including familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). The cumulative risk in developed countries is about 5% by the age of 75 years. The number of patients suffering from the disease will probably increase in the future because of aging of the population in developed countries. [1] There is no established way of preventing colon cancer and there is no cost-effective screening method at the moment.[2,3] In general, symptomatic patients are treated as they present themselves. In the end, for half of these patients cure won't be possible. However, approximately 80% of the patients are presented in a stage that is considered to be curable. Lymph node status is still the most important predictor of outcome. However, several molecular biological factors, including *TP53* mutation, the microsatellite instability (MSI) phenotype and TS and DPD mRNA expression seem to play an important role in the success of adjuvant treatment.[4-6] *TP53* has a negative impact on disease-free survival. In patients with high-frequency microsatellite instability (MSI-H) tumors, adjuvant chemotherapy will not significantly improve survival. The 5-year survival rate is 70-80% for patients with node negative disease (stage I/II), but only 45-50 % for those with node positive tumors (stage III).[7] Adenocarcinomas are by far the most common malignant tumors of the large bowel. Other bowel tumors include carcinoid tumors, lymphomas, gastrointestinal stromal cell tumors and metastases of primary tumors elsewhere. All of these tumors are rare. Sixty percent of colorectal cancers arise in the distal part of the large bowel, which is defined as distal to the splenic flexure. In recent years, however, more proximally located tumors have been diagnosed.[8] For the pathologist, colorectal cancer is heterogeneous, both macroscopically and microscopically. The lesions can be exophytic, polypoid or endophytic. Although endophytic lesions may present as a small intraluminal tumor, they usually show an extensive infiltration of the bowel wall. Under the microscope, most cancers are moderately differentiated, gland-forming adenocarcinomas. Mucinous or colloid cancers, which produce extensive amounts of mucin, and signet-ring cell adenocarcinomas, occur much less frequently. The primary treatment for colon cancer is a radical surgical resection.

However, even in radical resections of stage III tumors, small tumor deposits not detected with currently available techniques (micrometastases), are present. Until the 1980's the consensus was, that surgery was the best and only standard treatment. In the early nineties, Moertel et al. showed a clear benefit from multimodality treatment, including adjuvant fluorouracil and levamisole for patients with node-positive disease.[9] Since then, numerous new agents and combinations of therapy have evolved for palliative and adjuvant therapy.[10-20] Despite the favorable prognosis of patients with localized stage II colon cancer without regional lymph node metastasis, 20-30% of these patients will develop recurrent disease, even after apparently curative resection. Generally there are high and low risk groups within stage II colon cancer. One of the therapeutic challenges now and in the future is to find a better way to select these patients and to treat them appropriately with an individualized adjuvant regimen.

Pathology and carcinogenesis

The great majority of colon cancers develop from colon adenomas or adenomatous polyps. Adenomas are benign neoplastic lesions that arise from the colon epithelium. The origin of adenomas and thus carcinomas is genetic. Colon cancer develops through a multistep process with an accumulation of multiple genetic alterations that are often the cause of a form of genomic instability. The two best known mechanisms of genomic instability are chromosomal instability (CIN) and microsatellite instability (MSI).[5] The CIN pathway is characterized by changes in the cellular genome, such as aneuploidy, multiple chromosomal rearrangements and an accumulation of somatic mutations in several known oncogenes. The loss of function of two tumor suppressor genes, the adenomatous polyposis coli (APC) and the *TP*53 gene, is considered to be essential for the initiation and progression of colorectal carcinogenesis in this pathway.[21-24] The CIN phenotype is found in approximately 85% of sporadic colon cancers.[5] The remaining 15% of colorectal cancers display a phenotype with small insertions and deletions mainly in repetitive sequences (microsatellites). This form of genetic destabilization is most commonly caused by the loss of the DNA mismatch-repair function and is referred to as the microsatellite-instability pathway. The phenotype of tumors with this defect is termed the high-frequency-microsatellite-instability phenotype (MSI-H).[5,25-29] Distinct clinical and pathological features of colorectal tumors arising from these two separate mutational pathways have been identified. Mutations in the *TP*53 gene are associated with an aggressive tumor growth and

subsequent reduced survival.[5] MSI-H is observed more frequently in colon cancers that occur proximal to the splenic flexure. These MSI-H tumors mostly exhibit poor differentiation, mucinous cell type and peritumoral lymphocytic infiltration.[27,29] They have also been associated with a larger size of the primary tumor and a more favorable stage distribution.[30] Patients with the MSI-H phenotype have longer survival than stage-matched patients with chromosomal instability (CIN) tumors.[29-31] There are two well-known dominantly inherited cancer syndromes named familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). HNPCC is the most common hereditary cancer syndrome. It is inherited in an autosomal dominant manner. The prevalence of HNPCC in newly diagnosed colon cancer patients is 2-4%. Most tumors in HNPCC are characterized by microsatellite instability of tumor DNA (MIN-pathway).[28] A diagnosis of HNPCC should be suspected when patients with colon cancers have a positive family history of HNPCC related cancers, especially if the diagnosis was made before the age of 50 years. FAP is an autosomal dominantly inherited disorder characterized by the development of hundreds or thousands of adenomatous colorectal polyps during adolescence and early adulthood. Malignant transformation will occur in one or more of these polyps and invasive cancer will develop in most patients before the age of 40. The disease is due to mutations in the APC-gene (CIN-pathway). [23] Less than 1% of colon cancers are due to FAP.

Disease staging

Accurate staging of colon cancer is essential to clinical decision making and to prognosis. The American Joint Committee on Cancer (AJCC) has designated staging of cancer by the Tumor Node Metastasis (TNM) classification (Box 1).[32] T indicates the progressive degree (1-4) of invasion of the tumor into the bowel wall. N represents the nodal involvement and M indicates distant metastasis. Disease prognosis (without chemotherapy) derived from this staging process is shown in Box 2.

Box 1. TNM Staging

T	Primary tumor
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_1	Tumor invasion of submucosa
T_2	Tumor invasion of muscularis propria
T_3	Tumor invasion of subserosal fat
T4	Tumor invasion of other organs or structures and/or perforation of the visceral peritoneum
N_0	No lymph node metastases
N_1	Metastases in 1 to 3 regional lymph nodes
N_2	Metastases in 4 or more regional lymph nodes
M_0	No distant metastases
M_1	Distant metastases

Box 2. Stage grouping for colon cancer and prognosis

pTNM	Stage (AJCC)	5-year survival rate (%)
T_{1-2}, N_0, M_0	I	90
T_{3-4}, N_0, M_0	II	80
T_{1-4}, N_{1-2}, M_0	III	50
T_{1-4}, N_{1-2}, M_1	IV	5

THERAPEUTIC APPROACHES

Overall patient management

The prognosis of colon cancer is related to the degree of penetration of the tumor through the bowel wall and the presence or absence of lymph node involvement and distant metastases. Curative treatment involves a multi-modality approach, in which surgery is an essential part. Cure can be achieved in approximately 50% of resected patients without adjuvant chemotherapy.[33] Adjuvant chemotherapy is routinely administrated when lymph node metastases are present. In case of severe co-morbidity or extensive metastatic

disease, local palliative treatment modalities are frequently applied. This includes stenting for bowel obstruction and radiotherapy for bleeding and pain.[34,35] Following curative intended treatment of colon cancer, periodic evaluations in selected groups may lead to the early identification and management of asymptomatic recurrent disease.

Role of surgery and pathology

As already mentioned surgery remains the principal treatment modality for stage I to III colon tumors. The extent of the resection is determined by its location within the regional lymph drainage area. For tumors in the right colon (coecum/ascendening colon) a right hemicolectomy is performed. This includes resection of the last 10 cm of the terminal ileum and part of the transverse colon with ligation of the ileocolic artery, right colic artery and the right branch of the middle colonic artery. For tumors in or just distal of the hepatic flexure, a right extended hemicolectomy should be performed. This includes ligation of both branches of the middle colic artery. The whole transverse colon is resected when a tumor is located in the transverse colon. Tumors in the splenic flexure or the descending colon are usually treated by a left hemicolectomy, including the area supplied by the left colic artery and left branch of the middle colic artery. For sigmoid tumors a sigmoid resection is performed during which the superior rectal artery and its branching sigmoidal arteries are ligated. To prevent spill of tumor cells due to mobilization of the tumor, the 'no-touch' technique was developed. It should be noted that this is not a standard procedure in various countries. It involves early ligation (before mobilization) of the feeding artery and central vein. In a prospective study no significant survival benefit of this technique was shown, although it did show a decreased incidence of liver metastases.[36] Treatment of rectal tumors is beyond the scope of this review. Regional lymph nodes are removed en bloc with the resected colon. For adequate staging and treatment of patients with colon cancer, a meticulous histological examination of at least 12 nodes harvested by pathological analysis is warranted according international guidelines.[32]

Role and biological basis of fluorouracil based adjuvant chemotherapy

Thymidylate synthase (TS) has been used as a target for cancer chemotherapy in the development of fluoropyrimidines such as 5-fluorouracil (5-FU). However, the precise

mechanism by which TS inhibition leads to cell death is still not completely resolved.[37] TS inhibition results in depletion of dTTP, an essential precursor for DNA, and an increase in dUTP. This results in the so-called thymine-less death due to misincorporation of dUTP into DNA. Its excision, catalyzed by uracil-DNA glycosylase, results in DNA damage. Both this imbalance in dTTP/dUTP and DNA damage can result in induction of downstream events, leading to apoptosis.[37] On the other hand a specific interaction exists between oncogenes like *TP53* and *TS*. These complex indirect and direct interactions between oncogenes and *TS* may have as yet unclear clinical implications, since most data are based on in vitro or in vivo studies and some results are contradictive. Randomized trials in the 1980s demonstrated that fluorouracil (FU)-based adjuvant therapy could decrease the chance of death by approximately 30%.[9,38,39] Since then, FU-based adjuvant therapy is recommended for all medically fit patients with completely resected stage III colon cancer. For stage I patients, there are no relevant studies on the use of adjuvant therapy. The benefit of adjuvant therapy for patients with stage II colon cancer has long been an area of controversy. However, consensus guidelines on this subject have been published recently.[40] We will further discuss the use of adjuvant therapy in the subsequent stages of disease in the next paragraphs.

Stage III

In 1990, as mentioned before, Moertel and coworkers showed that fluorouracil (FU)-based therapy decreased the chance of death in stage III patients by approximately 30%, with a greater than 10% absolute benefit in 5-year survival.[9] They added levamisole, an antihelminthic immunomodulater, to the FU regimen. Later studies showed that the inclusion of levamisole in chemotherapy regimens for colorectal cancer does not delay recurrence or improve survival compared to the combination of 5-FU with leucovorin (Mayo regimen).[10,41] The addition of folinic acid or leucovorin (LV) seems to potentate the effects of FU. The supplementation of the intracellular reduced folate pool by folinic acid prolongs the competitive inhibition of TS by FU. [42]The benefits of the combination FU and leucovorin were supported by several studies.[15,43,44] The IMPACT trial published in 1995 demonstrated a disease free survival of 71% with the FU/leucovorin combination with an overall survival of 83%.[43] The Quick and Simple and Reliable (Quasar) study in 3239 stage II and III colon and rectal cancer patients, randomizing to either observation or bolus 5-FU plus leucovorin at low or high dose, or 5-FU plus levamisole, showed that higher dose

folinic acid produced no extra benefit over low-dose folinic acid with a significant survival benefit of 3% in the treatment group (p=0.02).[10] Survival rates were 70% with 3-year recurrence rates around 36%. These results were confirmed by Link et al who showed a 5-year overall survival rate of 60,5% for stage III patients treated with FU and levamisole versus 72 % if folinic acid was added to this schedule.[15] Furthermore, in the Intergroup 0089 study on 3759 colon cancer patients, 80% of whom were in stage III and 20% in high risk stage II, the 5-FU/low-dose LV (Mayo scheme) proved to be equivalent to 5-FU/ high-dose LV (Roswell Park scheme). Based on these studies and the relative high neurotoxicity of levamisole, which was standard treatment in the early 90's, this drug was abandoned in favor of leucovorin.[45] The oral fluoropyrimidines capecitabine and tegafur-uracil (UFT)/LV generate fluorouracil preferentially in tumor tissue with an equal activity as 5-FU/LV. The final stage of conversion to fluorouracil is catalyzed by thymidine phosphorylase, which is appreciably more active in tumor than healthy tissue. Twelves et al found that oral capecitabine (Xeloda) is an effective and at least equivalent alternative to intravenous FU plus leucovorin in the adjuvant treatment of stage III colon cancer. In addition, it was associated with significantly fewer adverse events than FU plus leucovorin.[20] An equal effect was found for UFT/LV compared to FU/LV.[46] Treatment of advanced CRC has dramatically been improved in the last decade due to the development of new treatment options, including irinotecan (CPT11) and oxaliplatin (L-OHP). Irinotecan is a semisynthetic camptothecin which inhibits topoisomerase I, impeding DNA uncoiling which leads to double-stranded DNA breaks. Oxaliplatin is a platinum-based drug, forming cross-linking adducts, which blocks DNA replication and transcription. Combination therapy of FU/leucovorin with irinotecan or oxaliplatin are effective in stage IV colon cancer, which will be discussed later.[47] Based on the results in advanced disease these new strategies have been used in an adjuvant setting in stage II/III colon cancer patients. However, in stage III colon cancer, the combination of irinotecan with an IV-bolus scheme of FU/leucovorin showed no survival benefit to FU/leucovorin alone.[48] From studies in stage IV patients treated with this combination scheme, it is known that the FU should be administered in a continuous infusion.[49] The results of this FOLFIRI scheme in stage III patients as an adjuvant therapy (Pan European Trial in Adjuvant Colon Cancer: PETACC-3 study; n=2111 pts) have not been published yet. Preliminary data show insufficient effect of the FOLFIRI schedule in stage III colon cancer, with a 3-year disease-free survival of 59,9% and 62,9% in FU/LV and FU/LV/Irinotecan, respectively.[50] Irinotecan seems to have a more additive effect with FU/LV, while oxaliplatin has a more synergistic effect. The Multicenter International Study of Oxaliplatin/5-FU/LV in Adjuvant Treatment of Colon Cancer (MOSAIC) trial included 2246

patients with stage II (40%) and III (60%) colon cancer. It evaluated the efficacy of adjuvant treatment with FU/leucovorin plus oxaliplatin (FOLFOX 4 schedule) versus FU/leucovorin alone. The DFS in the FOLFOX 4 schedule was 85,1% vs 81,3 in the FU/LV schedule. The absolute survival benefit for the FOLFOX schedule was 6,6%.[51] These results were confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 study which randomly assigned for LV/5-FU alone or combined with oxaliplatin (FLOX) in which 5-FU was given as bolus.[52] This study showed a significant better DFS at 3 years in the FLOX-group (76.5% vs 71.6%, p=0,04) and a 23% reduction in recurrence risk. Based on the above mentioned results FOLFOX became the treatment of choice in the adjuvant setting, although the incidence of myelosupression and neurotoxicity is relatively higher compared to 5-FU/LV alone. These studies also suggest oxaliplatin to be of benefit independent of 5-FU/LV administration. Whether the substitution of 5-FU/LV by oral alternative equivalents including capecitabine will be beneficial is currently under investigation as first-line therapy.[53] Results of the major trials are summarized in table 1.

Table 1. Results of FU based adjuvant therapy in stage II and III colon cancer

Treatment	Disease stage	Number of patients	Disease free survival rate (%)*	p-value	Ref
None vs FU/levamisole(Lev)	II and III	1269	47 vs 63	<0,0001	9
None vs FU/leucovorin(LV)	II and III	1526	62 vs 71	<0,0001	38
FU/Lev vs FU/Lev/LV	II and III	891	60 vs 70	<0,01	39
FU/Lev/LV vs FU/LV	I,II,III	4927	63 vs 65	0,06	10
FU/Lev vs FU/Lev/LV	III	855	57 vs 66	0,0004	15
FU/LV vs capecitabine	III	1987	60 vs 64	0,12	20
FU/LV vs FU/LV/oxaliplatin	II and III	2246	72,9 vs 78,2	0,002	11

*3- or 5-year survival

Stage II

As mentioned in the introduction, the benefit of adjuvant therapy for patients with stage II colon cancer has long been an area of controversy. Too few stage II patients have been included in most trials to determine whether they derive a small benefit from FU-based postoperative therapy. The trials that include higher numbers of patients show conflicting results.[54-58] The results of the trials are summarized in table 2. The varying results between the trials might be explained by differences in the study populations. It is possible that there is a difference between the studies in the proportion of patients with poor prognostic indicators such as bowel obstruction, perforation, adhesion to adjacent organs and in those cases with <12 lymph nodes examined in the pathology report. Patients with these characteristics are classified as high risk patients. Because the number of high risk stage II patients is usually low in the study population, it is unlikely that significant survival differences are found when administering chemotherapy. In the NSABP pooled analysis a 5% disease free survival difference was found after adjuvant therapy between high and low risk stage II patients.[56] Andre et al, using the FOLFOX schedule, also found a 5% disease free survival difference. Both studies did not reach significance, probably because of insufficient numbers. The American Society of Clinical Oncology (ASCO) recently published guidelines on this subject, in which the routine use of adjuvant chemotherapy is not supported in node-negative patients. However, they did find indirect evidence of benefit for patients with high-risk disease. [40] We have to refine the category of patients with stage II colon cancer who may benefit from adjuvant treatment. At least 12 lymph nodes have to be examined to consider the tumor as node negative. Whether the sentinel node procedure will be valuable is still a matter of debate

Table 2. Results of FU based adjuvant therapy in stage II colon cancer

Number of patients	survival rate (%)*	p-value	Ref
1116	82 vs 80	NS	54
1565			56
-26% high risk*	75 vs 70	NS	
-74% low risk	87 vs 82	0,01	
318	72 vs 72	NS	57
1029	78 vs 70	0,007	58
3238	80 vs 77	0,06	55
576	84,9 vs 79,8	NS	11

*high risk: obstruction, perforation, T4

Table 3. Results of FU based therapy in stage IV colon cancer

Schedule	Number of patients	Median survival	Ref
None vs FU/LV or FU/Lev	1365	8 vs 11-12	59
FOLFIRI/FOLFOX vs FOLFOX/FOLFIRI	220	20,6 vs 21,5	49
FU/LV/irinotecan vs FOLFOX	531	15,0 vs 19,5	13
FU/LV/irinotecan vs FU/LV/irinotecan/bevacizumab	1029	15,6 vs 20,3	61
FU/LV vs FU/LV/bevacizumab	500	17,9 vs 14,6	62
Cetuximab vs cetuximab/irinotecan	329	6,9 vs 8,6	12

Stage IV

Although the treatment of stage IV patients is beyond the scope of this review on adjuvant 5-FU based chemotherapy, we would like to discuss it shortly. Palliative chemotherapy commonly increases the median survival of stage IV colon cancer patients from around 8 months without treatment to 12 months with FU/leucovorin therapy.[59] Better results could be achieved with the new generation of chemotherapeutic agents like irinotecan and oxaliplatin showing median survival periods of 20- 21 months.[13,47,49] Recently, the Dutch Colorectal Cancer Group finished inclusion of 820 patients in the CAIRO study, in which a sequential approach of 5-FU/LV, CPT-11 and oxaliplatin in phase III trials showed promising results in patients with metastatic disease, with a prolonged survival of more than 20 months. In a prospective study, Adam et al used a combination of FOLFOX/chronomodulated chemotherapy to obtain reduction of tumor load in patients with non-resectable liver metastases. After chemotherapy, 13.5% of patients were found to be resectable on re-evaluation and underwent a potentially curative resection. The 5-year survival was 35% in this group.[60] The development of drugs that inhibit signal transduction pathways have provided new opportunities in treating metastatic colon cancer. The concept of targeting tumor vasculature as a therapeutic strategy in human cancer was based on the observation that rapid growth of transplanted tumors was often preceded by a local increase in vascular density. This is called angiogenesis. One of the most potent mediators of angiogenesis is vascular endothelial growth factor (VEGF). VEGF mediates its effects by interacting with the membrane-bound tyrosine kinase receptors, thereby influencing angiogenesis. Bevacizumab is the recombinant humanized version of a murine antihuman VEGF monoclonal antibody. Several studies showed a beneficial effect of bevacizumab in combination with FU-based chemotherapy in patients with stage IV colon cancer.[61,62] In patients with metastatic disease the combination of bevacizumab and CPT-11/5-FU/LV should be considered as first-line treatment. Another example of anti-tumor therapy by inhibiting signal transduction is the inhibition of the epidermal growth factor receptor (EGFR). The EGFR signaling pathway regulates cell differentiation, proliferation, migration, angiogenesis and apoptosis, all of which become deregulated in cancer cells. Cetuximab is a chimeric IgG1 monoclonal antibody that binds to EGFR with high specificity and with a higher affinity than EGF, thereby blocking ligand-induced phosphorylation of EGFR. Cunningham et al showed that cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer.[12] This study suggests that cetuximab may circumvent irinotecan

resistance. Studies on palliative treatment in stage IV colon cancer are summarized in table 3.

Treatment toxicity

Dihydropyrimidine dehydrogenase (DPD), the first and rate-limiting enzyme in the three-step pathway of uracil and thymine catabolism, is also important in the degradation and inactivation of 5-FU.[63] DPD converts over 85% of the clinically administered 5-FU into the inactive metabolite dihydrofluorouracil, a process which takes place mainly in the liver. [64] Patients with a complete or near-complete deficiency of the enzyme do suffer from severe toxicity following the administration of standard doses of fluoropyrimidines, due to significantly increased and prolonged plasma levels of 5-FU.[63-65] The incidence of this pharmacogenetic syndrome in the general population is estimated to be as high as 3% and may be much more common than originally thought.[66] The use of fluoropyrimidines in patients with this metabolic defect is associated with a very high mortality.[64] The most common toxic reactions in patients without a known DPD deficiency to FU are nausea, vomiting, diarrhea, stomatitis, dermatitis and leucopenia. These reactions were rarely in the range of grade 3-4 toxicity in the study of Moertel et al. [9] This same study showed that 22% of patients experienced some degree of alopecia. A variety of neurological symptoms was reported by 18% of patients. These ranged from vague lightheadedness and emotional changes to disabling cerebellar ataxia. They usually abated when therapy was discontinued. 3% of patients developed severe leukopenia (WBC< 1000). The combination of FU with leucovorin increases some toxicity effects of FU, especially nausea; diarrhea and stomatitis are more often seen. The International Multicenter pooled Analysis of Colon Cancer (IMPACT) trial showed that severe toxic effects (WHO grade 4) occurred in fewer than 3% of cases with a combined FU/LV treatment.[43] Capecitabin and UFT, which are chemically related to FU showed significantly fewer side effects than FU.[20,46] One of the most frequent side effects of Capecitabin is the hand-foot syndrome in which the skin of hands and feet is affected. The FOLFOX regimen leads to a significantly higher rate of grade 3-4 leukopenia and neuropathy compared to FU/leucovorin alone (41 vs 5% and 12 vs 0,2%).[11] This neurotoxicity is a typical side effect of oxaliplatin and is usually reversible. The total prevalence of neurotoxicity in the FOLFOX study was 82%, of which 12 % consisted of a grade 3 toxicity. After 12 months follow up this rate decreased to 1,1% for grade 3 toxicity and 4,8% for grade 2 toxicity. The signal transduction inhibitors (bevacizumab and

cetuximab) do not cause major side effects in combination with the other agents. Bevacizumab caused grade 3 hypertension in 16% of FU/leucovorin/bevacizumab treated patients. In addition, proteinuria was seen more often with bevacizumab. There was also a disbalance in the incidence of arterial thrombotic events with an increased occurrence in the group with bevacizumab (10 vs 5%). No increase in grade 3 or 4 bleeding or venous thrombotic events was seen in bevacizumab treated patients. Two patients (2%) developed gastrointestinal perforation. [62] Cetuximab caused severe anaphylactic reactions in 1,2% of patients. An acne-like rash developed in about 80% of the patients, but grade 3 or 4 toxic effects on the skin were observed in only 9% of patients. [12]

Summary of current available strategies of adjuvant chemotherapy treatment

Approximately 80% of the patients present with colon cancer in a stage that is considered to be potentially curable. Lymph node status is the most important predictor of outcome. The principal treatment for stage I, II and III tumors is surgery. In patients with stage II colon cancer, the use of adjuvant chemotherapy is debatable. The routine use of adjuvant chemotherapy is not supported by the ASCO in node-negative patients. However, there is indirect evidence of benefit for patients with high-risk stage II disease including bowel obstruction, perforation, T4 stage and less than 12 examined lymph nodes in the pathology report.[40] Systemic adjuvant therapy is standard treatment for stage III colon cancer and should consist of FU, leucovorin and oxaliplatin when possible.[11] Individual exceptions based on age and coexisting diseases are possible. Capecitabin and UFT are effective alternatives to FU/leucovorin in Stage III patients.[20,46] Fluoropyrimidines, irinotecan and oxaliplatin have efficacy in the management of metastatic colorectal cancer. Combinations of therapy can increase the median survival time from 8 to 20 months.[49,67] Neo-adjuvant treatment with the FOLFOX regimen is possible in patients with non-resectable stage IV disease, and can downsize non-resectable metastases to resectable metastases.[60] Targeting of the EGF-Receptor and VEGF-receptor is currently the most promising biological approach.

Future directions

In adjuvant treatments, the group that does not benefit from therapy consists of patients who were qualified for adjuvant therapy but in spite of this still developed metastases and

patients who would never develop metastases in the spontaneous course of their disease (with or without this adjuvant treatment). The ratio between patients subjected to the side effects of therapy without any benefit and the patients who do benefit from chemotherapy is 5:1.[68] The great challenge for the future is to develop better selection criteria for adjuvant treatment, thereby reducing the group of patients who do not benefit at all from the treatment.

Better staging detects more lymph node positive patients and immunohistochemistry might help to detect stage II patients at higher risk. It is well known that the 5-year survival in node-negative patients is significantly higher when more lymph nodes have been examined.[69] Therefore, surgeons and pathologists should be stimulated to harvest and examine as much lymph nodes as possible. For adequate staging and treatment of patients with colon cancer, meticulous examination of at least 12 nodes by pathological analysis is warranted.[32] However, with a fat-clearance technique a mean number of 50 lymph nodes per specimen can be found.[70] In addition, intensive pathological examination of lymph nodes may reveal micrometastases that would be missed by routine hematoxylin & eosin (H&E) examination. Several authors have reported a decreased survival rate when nodal micrometastases are detected in CRC.[71,72] Based on the above mentioned studies, we can readily assume that the pathologist only samples a small part of the regional lymph nodes, and will certainly miss some lymph node metastases. The intensive staging techniques are time consuming, labor intensive and costly. The sentinel node procedure might select the right lymph nodes for intensive pathological examination, which will save time and money. The procedure has been validated in large studies.[73-75] It is a relatively simple procedure which only takes 5-10 minutes during surgery.

Besides ultrastaging, we should probably exploit our knowledge of tumor genetics and biology. A start in this area has already been made by treating stage IV colon cancer patients with signal transduction inhibitors like bevacizumab (anti-VEGF) and cetuximab (anti-EGFR).[12,61] These drugs still need to be tested in stage II and III patients.

Molecular biological factors might help to better select stage II + III patients at risk and those who are sensitive to and benefit from 5-FU based adjuvant therapy. This has already been done in breast cancer. [76-78] Wang et al found a combination of gene expression in colon cancer that predicted a 13-fold increased risk of relapse in stage II patients. These patients were selected for adjuvant therapy.[79] The results of this study still need to be evaluated in a larger study.

Genetically determined variability of the function of certain key enzymes has been shown to influence toxicity and response to certain types of chemotherapy and survival.[80] For example, patients with high thymidylate synthase gene expression profit from adjuvant therapy.[6;81] Patients with low thymidylate synthase expression and adjuvant therapy seem to have a worse prognosis than surgery alone.[81] This seems to be different from the situation in palliative 5-FU based chemotherapy.[82] Patients with colon tumors exhibiting high-frequency microsatellite instability do not benefit from FU-based chemotherapy.[4] Volk et al published a case report on an alternative chemotherapy regimen which was very well tolerated in a DPD-deficient patient.[83] More future trials should incorporate these genetic tumor variations in the choice of therapy.

In summary, better selection of patients should lead to a more targeted therapy in the future.

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